AWARD NUMBER: W81XWH-14-1-0453

TITLE: Genetic Variations in SLCO Transporter Genes Contributing to Racial Disparity in Aggressiveness of Prostate Cancer

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REPORT DATE: October 2016

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2016	Annual	15 Sep 2015 - 14 Sep 2016

4. TITLE AND SUBTITLE

Genetic Variations in SLCO Transporter Genes Contributing to Racial Disparity in Aggressiveness of Prostate Cancer

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-14-1-0453

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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Buffalo, NY 14263-0001

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The proposed studies are expected to (1) identify genetic variations in the genes of androgen transporters that are associated with the racial differences in prostate cancer aggressiveness; (2) identify key androgen transporters of which the expression and/or the alteration of expression in cancer relative to benign prostate tissue are associated with racial differences in prostate cancer aggressiveness. Progress in the reporting period includes: 1) Completion of genotyping for all 11 SLCO members using PCaP DNA samples; 2) Finish data processing and preliminary data analyses for genotyping, and identified SNPs that may be associated with prostate cancer characteristics; 3) Continued RNAScope analysis of SLCO transporter in prostate cancer tissue sections and discover unique cell type-specific expression of a SLCO transporter; 4) Further delineation of androgen uptake mechanism on molecular levels.

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	30	19b. TELEPHONE NUMBER *(include area code)*

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1. INTRODUCTION

Compared to European American (EA) men, African American (AA) men suffer higher incidence of, and greater mortality rate from prostate cancer. Results of multiple studies indicate that prostate cancer in AA men may progress faster than prostate cancer in EA men, and thereby becomes more aggressive. This study is focused specifically on identification of genetic/biological culprits that cause more aggressive types of prostate cancer in AA men. In particular, the proposed studies are focused on the question of how differences in transporter-mediated androgen uptake may contribute to the more aggressive type of prostate cancer in AA versus EA. The proposed studies are expected to (1) identify genetic variations in the genes of androgen transporters that are associated with the racial differences in prostate cancer aggressiveness; (2) identify key androgen transporters of which the expression and/or the alteration of expression in cancer relative to benign prostate tissue are associated with racial differences in prostate cancer aggressiveness.

2. KEYWORDS

Prostate cancer, health disparity, androgen, transporter, genetic variation.

3. ACCOMPLISHMENTS

What were the major goals of the project?

Specific Aim 1: DNA samples as well as relevant clinical and epidemiological data will be requested for 2258 cases (1130 AA and 1128 EA) from the North Carolina-Louisiana Prostate Cancer Project (PCaP). A total of 952 SNPs along with a panel of 50 ancestry informative markers (AIMs) will be used for genotyping of 11 SLCO transporters. Genotyping will be performed via the GoldenGate Assay by Illumina Bead Station System in the Genomics Core Facility at Roswell Park Cancer Institute (RPCI).

A total of four Subtasks were proposed for Specific Aim 1 in Year 1 and Year 2 (months 1-18):

Subtask 1 (months 1-3): Obtain approval for IRB protocol and request clinical data and blood DNA samples from the PCaP.

Subtask 2 (months 4-10): Genotype 11 SLCO transporters.

Subtask 3 (months 11-14): Analyze data and to determine the association of genetic variants with prostate cancer aggressiveness.

Subtask 4 (months 15-18): Summarize data and develop a manuscript.

Subtask 1 has been completed in Year 1. The goals for Year 2 were to complete subtasks 2-4.

Specific Aim 2 is to examine in situ expression profiles of SLCO transporters in prostate tissue and investigate associations of the expression profiles with prostate cancer aggressiveness in AA and EA. Expression of SLCO transporters at transcriptional levels will be examined first in tissue microarrays (TMAs) constructed from prostate cancer and distant benign tissues of 92 AA and 92 EA patients from the Pathology Resource Network (PRN) at Roswell Park Cancer Institute (RPCI). The predominantly expressed SLCO transporters in AA or EA, and the transporters with expression significantly altered in cancer relative to benign tissues, will be selected and expression at protein levels will be examined using immunohistochemistry (IHC) on TMAs requested from the PCaP. The data on expression will be combined with the data on disease characteristics from the PCaP to investigate associations of the expression profiles with prostate cancer aggressiveness in AA and EA.

A total of 4 Subtasks proposed for Specific Aim 2 for Year 1 and Year 2 (Months 7-24):

Subtask 1(months 7-10): Obtain approval for IRB protocol and request clinical data and TMAs from RPCI and PCaP.

Subtask 2 (months 11-18): Characterize gene expression profiles of SLCO transporters at mRNA levels on TMAs from RPCI using quantitative in situ RNA hybridization technology RNAScope.

Subtask 3 (months 19-20): Analyze data from RNAScope and identify candidate transporters.

Subtask 4 (months 21-24): Confirm expression of the identified candidate transporters at protein level using IHC staining.

Subtask 1 has been completed in Year 1. Goals for Year 2 were to complete subtasks 2-4.

Specific Aim 3 will characterize functions of candidate SLCO transporters in androgen uptake and evaluate the biological effects on AR signaling in human prostate cancer cell lines. Based on the findings from Aim 1 and Aim 2, candidate SLCO transporters will include the transporters that are predominant in either AA or EA, show significantly altered expression between tumor and benign tissue, or harbor genetic variants that are significantly associated with prostate cancer aggressiveness. Relevant cell models will be constructed using over-expression or siRNA knock-down for functional analysis. Although all research activities of **Aim 3** were proposed for Year 3 (Months 25-36), preliminary work such as experimental condition optimization and androgen uptake mechanism delineation were carried out through Year 1 and Year 2 in order to use fund more efficiently.

What was accomplished under these goals?

Aim 1. Genotyping was successfully completed. To comprehensively examine single nucleotide polymorphisms (SNPs) in genes of all 11 SLCO transporters, two types of SNPs were selected: tag SNPs selected for African American (AA) and European American (EA) population separately based on Hapmap data with minor allele frequency of at least 0.05, and potential functional SNPs selected from the literature. To control for potential bias due to population admixture, a panel of 128 ancestry informative markers (AIMs) were included. A custom 1,152-OPA was assembled and the breakdown number of SNPs for each gene was presented in Table 1. A total of 2159 participants with sufficient DNA samples and clinical data were identified and requested from PCaP. The samples were randomly plated onto 24 96-well plates along with 96 duplicates and one set of in-house trio samples for quality control purpose. Genotyping was performed using an Illumina GoldenGate assay at the Genomics Core Facility at Roswell Park Cancer Institute (RPCI).

Table 1. The number of SNPs tested for each gene

Gene	# of SNPs
AIM	128
other	8
SLCO1A2	99
SLCO1B1	102
SLCO1B3	51
SLCO1C1	63
SLCO2A1	79
SLCO2B1	63
SLCO3A1	300
SLCO4A1	40
SLCO4C1	44
SLCO5A1	134
SLCO6A1	41
Total	1152

Results of 44 participants were excluded from the analysis due to withdrawal of consent (2%). Results of another 65 participants (3%) were further removed during the quality control due to call rate <90% (59), abnormal heterozygosity (1), and unintended relatedness (2). A total of 2050 individuals (993 AA and 1057 EA) were included in the final analysis with an average call rate above 95%. Out of 1152 SNPs, 107 (9.3%) were removed from either AA or EA analysis due to call rate <90% (106) and violation of Hardy-Weinberg Equilibrium (1), resulting in 1045 SNPs in the final analysis with an average call rate above 95%.

Table 2 summarizes the descriptive characteristics of the study population by self-reported race. Comparing with EA men, AA men tended to be diagnosed at younger ages and were more likely to have prostate cancer with high aggressiveness. There was no difference in other tumor characteristics including primary and sum Gleason Grade as well as clinical stage. AA and EA men had similar rate of family history of prostate cancer, showing the majority (approximately 75%) had no family history. The self-reported race status was supported

by the distribution of ancestry proportions with the minimum of Asian ancestry in the study population. Therefore, either African or European ancestry proportion was adjusted in race-specific analysis but Asian ancestry was no longer considered. To note, the ancestry component information was requested from PCaP. Our own panel of AIMs generated similar estimates and further confirmed the validity of ancestry analysis.

Table 2. Descriptive and tumor characteristics by race

	African American (N=993)		European American (N=1057)		P_value*
	Mean	SD	Mean	SD	
Age at diagnosis, yrs	61.9	7.8	64.2	7.9	<0.001
European ancestry	0.08	0.15	0.97	0.07	<0.0001
African ancestry	0.90	0.16	0.01	0.04	<0.0001
Asian ancestry	0.02	0.05	0.02	0.05	0.687
	N	%	N	%	
Study site					0.416
North Carolina	436	43.9%	483	45.7%	
Louisiana	557	56.1%	574	54.3%	
1st Degree family history of prostate cancer					0.245
No	740	74.5%	811	76.7%	
Yes	253	25.5%	246	23.3%	
Primary Gleason Grade					0.082
<4	770	80.0%	858	83.0%	
≥4	193	20.0%	176	17.0%	
Gleason Grade Sum					0.147
<8	861	86.9%	936	89.0%	
≥8	130	13.1%	116	11.0%	
Stage					0.825
T1/2	946	98.1%	1019	98.3%	
T3/4	18	1.9%	18	1.7%	
Aggressiveness					0.0007
Low/Intermediate	750	79.0%	872	84.9%	
High	199	21.0%	155	15.1%	

* Chi square test was used for categorical variables, and student t-test was used for continuous variables if normally distributed, otherwise Kruskal-Wallis test was used.

Allele frequencies of these SNPs were compared by self-reported race. Of the 1045 SNPs tested, 780 (74.6%) displayed significantly different allele frequencies based on Fisher exact test with P values corrected by conservative Bonferroni method. These SNPs were further examined in relation to tumor characteristics. The primary outcome is prostate cancer aggressiveness, which is defined using three variables described as following: (i) high aggressiveness (Gleason sum ≥ 8 or PSA > 20 ng/mL or Gleason sum ≥ 7 and clinical stage T3–T4), (ii) low aggressiveness (Gleason sum < 7 and clinical stage T1–T2 and PSA < 10 ng/mL), and (iii) intermediate aggressiveness (all other cases). This characteristic has been described previously in the PCaP study and is associated strongly with survival. To access the associations between genotypes and prostate cancer aggressiveness (high versus intermediate/low), analysis was performed in AA and EA separately using logistic regression model adjusting for age, study site, family history of prostate cancer and African ancestry proportion. A co-dominant (genotypic) model was primarily assumed, then a dominant model was included with consideration of small number of homozygotes for most of tested SNPs. Odds ratios (OR) and 95% confidence intervals (CI) are shown in Table 3, along with three P values: P_trend, for genetic dose response by coding genotypes as 0, 1, 2 on the basis of the number of variant alleles; P_adj, P_trend after gene-based Bonferroni correction for the number of SNPs tested per gene; and P_interaction, Wald test of the product term between race and genotype for the differences in associations between AA and EA men. All analyses were performed using R and/or SAS 9.4 (Cary, NC). Since Bonferroni correction is a very conservative method, we present SNPs with corrected P_trend below the level of 0.1. As shown in Table 3, three SNPs fall into this category: rs7261643 in SLCO4A1 in EA men, rs10770742 in SLCO1B3 and rs9917636 in SLCO2A1 in AA men. After gene-based Bonferroni correction, only rs10770742 in SLCO1B3 retained a significant association with aggressiveness, showing that the variant (A allele) is associated with a reduced odds of high-aggressiveness prostate cancer among AA men (GA/AA versus GG, OR=0.53, P_adj=0.04). The inverse association between rs10770742 and prostate cancer aggressiveness was only observed among AA men, but not EA men with P_interaction < 0.0001. We further explored associations of genetic variations in SLCO transporters with other prostate cancer characteristics including primary Gleason Grade (≥4 versus <4), Gleason Grade Sum (≥8 versus <8) and clinical stage (T3/4 versus T1/2). The SNP rs10770742 in SLCO1B3 was again

associated with high Gleason Sum (GA/AA versus GG, OR=0.50, P_adj=0.008) and again the association was only observed among AA men but not EA men (P_interaction=0.001). Significant associations were also observed for rs7165104 in SLCO3A1 with Gleason Grade sum and rs4370538 in SLCO5A1 with clinical stage. Interesting, all the significant associations between genetic variations in SLCO transporters and tumor characteristics were only observed among one racial population showing significant P_interaction between AA and EA men. As mentioned previously, Bonferroni correction method is very conservative. Consequently some other significant SNPs might have been excluded. We are currently working with our statistician to explore other methods for correction of multiple comparisons such as FDR and permutation. We are also interested in gene-level analysis with combined genetic information per gene in relation to prostate cancer aggressiveness and other tumor characteristics. The project is moving forward as planned.

Table 3. Differential associations of single-nucleotide polymorphisms in SLCO transporters with prostate cancer characteristics between African American and European American men in the PCaP study

				European American				African American				
Gene	**SNP**	**Chr**	**Genotype**	**# high vs low**	**OR (95% CI)[a]**	**P_trend[a]**	**P_adj[b]**	**# high vs low**	**OR (95% CI)[a]**	**P_trend**	**P_adj[b]**	**P_interaction[c]**
Aggressiveness High vs. Low/Intermediate												
SLCO4A1	rs7261643	20	GG	87/599	1.00	0.007		154/589	1.00	0.811		0.419
			GA	56/238	1.67 (1.15-2.42)			45/154	1.13 (0.78-1.65)			
			AA	11/35	2.21 (1.07-4.57)			0/7				
			GA/AA vs. GG	67/273	1.74 (1.22-2.48)	0.002	0.066	45/161	1.08 (0.74-1.58)	0.671		
SLCO1B3	rs10770742	12	GG	33/261	1.00	0.06		47/108	1.00	0.004		<0.0001
			GA	88/421	1.69 (1.1-2.61)			91/408	0.5 (0.33-0.75)			
			AA	34/190	1.44 (0.85-2.42)			60/234	0.58 (0.37-0.9)			
			GA/AA vs. GG	122/611	1.61 (1.06-2.44)	0.025		151/642	0.53 (0.36-0.78)	0.001	0.04	
SLCO2A1	rs9917636	3	AA	33/231	1.00	0.099		62/150	1.00	0.002		0.005
			AG	88/417	1.49 (0.96-2.30)			93/367	0.6 (0.41-0.87)			
			GG	34/222	1.02 (0.61-1.72)			44/233	0.46 (0.3-0.71)			
			AG/GG vs. AA	122/639	1.32 (0.87-2.00)	0.194		137/600	0.55 (0.38-0.77)	0.001	0.073	
Primary Gleason Grade ≥4 vs. <4												
SLCO2A1	rs9917636	3	AA	43/219	1.00	0.243		60/157	1.00	0.005		0.03
			AG	96/420	1.17 (0.78-1.74)			85/379	0.57 (0.39-0.83)			
			GG	37/217	0.82 (0.5-1.33)			48/234	0.53 (0.35-0.82)			
			AG/GG vs. AA	133/637	1.04 (0.71-1.53)	0.83		133/613	0.55 (0.39-0.79)	0.001	0.073	
Sum Gleason Grade ≥8 vs. <8												
SLCO3A1	rs7165108	15	GG	82/778	1.00	0.001		109/658	1.00	0.198		0.001
			GA	30/139	2.15 (1.35-3.42)			20/184	0.67 (0.4-1.1)			
			AA	3/8	3.9 (0.99-15.37)			1/14	0.38 (0.05-2.93)			
			GA/AA vs. GG	33/147	2.25 (1.43-3.52)	<0.0001	<0.0001	21/198	0.64 (0.39-1.05)	0.08		
SLCO1B3	rs10770742	12	GG	24/276	1.00	0.102		33/128	1.00	0.009		0.001
			GA	66/456	1.72 (1.05-2.82)			63/457	0.52 (0.32-0.82)			
			AA	26/204	1.5 (0.83-2.7)			34/275	0.48 (0.28-0.81)			
			GA/AA vs. GG	92/660	1.65 (1.02-2.65)	0.04		97/732	0.5 (0.32-0.78)	0.002	0.008	
Stage 3/4 vs. 1/2												
SLCO5A1	rs4370538	8	AA	10/901	1.00	0.001		6/468	1.00	0.375		0.195
			AG	8/113	6.6 (2.52-17.32)			10/414	1.91 (0.68-5.39)			
			GG	0/3				2/64	2.5 (0.48-12.9)			
			AG/GG vs. AA	8/116	6.3 (2.41-16.5)	<0.0001	<0.0001	12/478	1.99 (0.73-5.43)	0.177		
SLCO2A1	rs7617777	3	AA	15/383	1.00	0.004		3/163	1.00	0.848		0.081
			AG	2/458	0.12 (0.03-0.51)			6/388	0.82 (0.2-3.35)			
			GG	1/178	0.14 (0.02-1.07)			9/391	1.11 (0.29-4.23)			
			AG/GG vs. AA	3/636	0.12 (0.04-0.43)	0.001	0.073	15/779	0.97 (0.28-3.44)	0.966		

[a] ORs and P_trend were estimated from co-dominant and dominant models adjusting for age at diagnosis, state (NC or LA), 1st degree family history of prostate cancer (yes/no), African ancestry component.

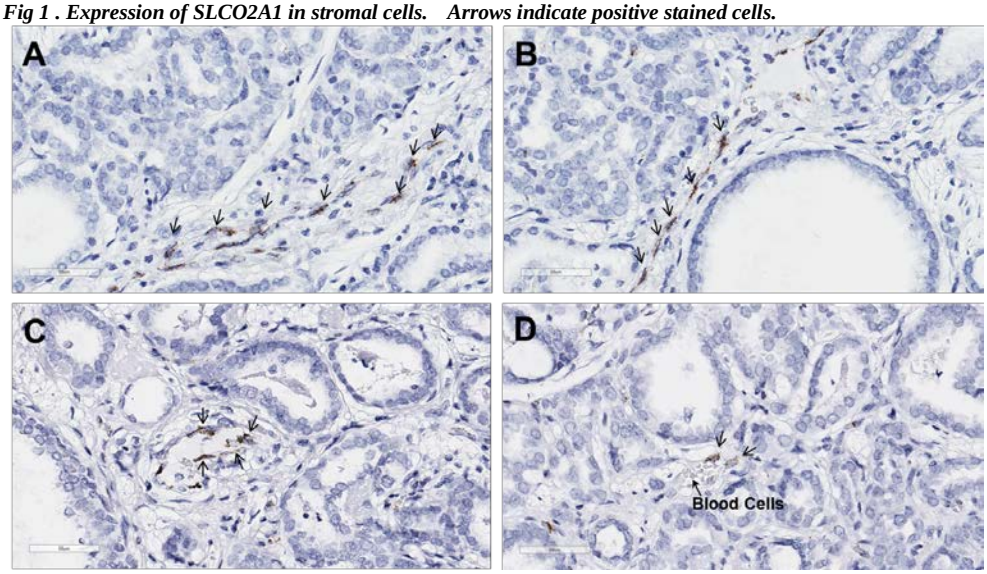
[b] P_adj was generated from P-trend after gene-based Bonferrroni correction, and only P_adj less than 0.1 was provided.

[c] P_interaction was for the differences in ORs between AA and EA men.

Aim 2. In Year 1, Conditions for IHC (for gene expression at protein levels) and RNAScope (for gene expression at mRNA levels) staining were optimized using a TMA set. We also validated antibodies for SLCO4A1 and SLCO5A1 and RNAScope probe for SLCO2B1. According to our preliminary data, SLCO2A1, 4A1, and 5A1 are the three SLCO members that are expressed at the highest mRNA levels in prostate tissue. In addition, preliminary analysis of genotyping data acquired in Year 2 indicated that genetic variations of SLCO 4A1 and 2A1 transporters may be associated with certain prostate cancer characteristics. Therefore, we re-

focused the tasks for Aim 2 by validating SLCO2A1 RNAScope probe using prostate cancer tissue FFPE sections before requesting the RPCI 92 EA/AA TMA for IHC and RNAScope staining. RNAScope probe for SLCO2A1 proved to work properly in a TMA that contains 10 matched benign and cancer tissue specimens of the prostate, and in prostrate cancer FFPE sections (Figure 1). An unexpected result was that the expression of SLCO2A1 did not preside in cancer cells or epithelial cells, instead, the transporter was expressed in stromal cells. The SLCO2A1 expressing cells formed continuous lines (Figure 1A-B) or circles (Figure1 C-D) in the stroma that surrounded benign and cancerous glands. Preliminary examination of the staining result by Dr. Gissou Azabadftari, a pathologist and co-investigator, revealed that the cells that express SLCO2A1 are likely to be endothelial cells. The staining patterns of lines or circles were resulted from side-way or cross-section perspectives. This unexpected finding is of importance. First, previous work by other groups using qRT-PCR approach to examine expression of SLCO members in prostate cancer and benign tissue could not discern cell types that express the transporters because RNA was prepared from whole tissue. We were able to distinguish cell types that express the transporters using RNAScope. Therefore, interpretation of these results by other groups needs to be reconsidered. More important, specific expression of SLCO2A1 in the stromal compartment such as endothelium indicate the involvement of the transporter in tumor microenvironment, and in regulating transit of circulating androgens to the prostate organ. Functional genetic variants may affect indirectly the availability of androgen to prostate cancer cells through such endothelial androgen regulatory mechanisms. Finding of RNAScope staining of SLCO2A1 echoed the results of RNAScope staining of SLCO2B1 in Year 1. Due to the likelihood of expression of both transporters primarily in endothelium, we decided to verify the findings by staining serial FFPE sections with the RNAScope probes and an antibody against CD31, an endothelial cell marker. The information is important to prepare us when moving forward to IHC/RNAScope staining of the RPCI 92 EA/AA TMA and PCaP TMA. This work is ongoing and we expect data in the end of October. In summary, through the continued effort on RNAScope in Year 2, we have validated the IHC and RNAScope methods of evaluating the expression of the 3 SLCO transporters of the highest expression levels in the prostate, and made a potentially important discovery that may redefine the underlying mechanisms that regulate androgen availability to prostate cancer cells.

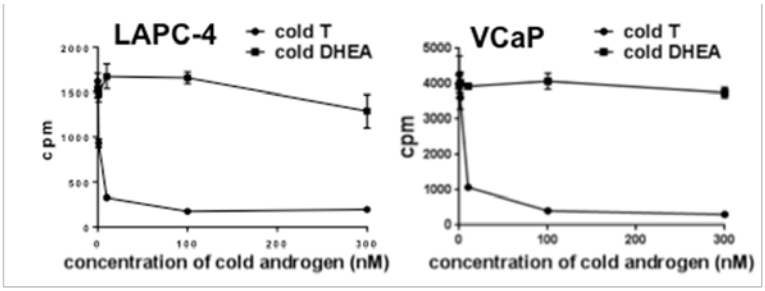
Fig 1 . Expression of SLCO2A1 in stromal cells. Arrows indicate positive stained cells.



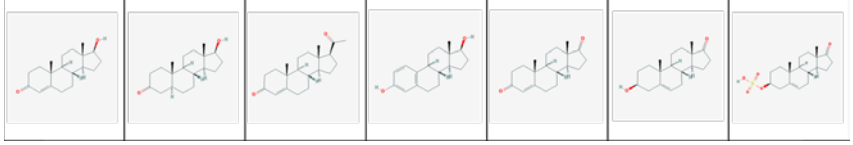
Aim 3. In Year 1, experimental conditions including time course, reagents, and doses of androgens were identified using a panel of human prostate cancer cell lines. In Year 2, study on mechanism for androgen uptake was continued using the established methods to examine competitive effect of steroids on testosterone (T) uptake and to identify subcellular localization of the uptake transporting mechanisms. The acquired knowledge will help better understand the role of transporters in androgen metabolism in prostate cancer cells in the aspect of steroid specificity. It is important to address whether the same uptake mechanism is used for

testicular androgens T and dihydrotestosterone (DHT), which are AR ligands, and for adrenal androgens dehydroepiandrosterone (DHEA), androstenedione (ASD), and DHEA sulfate (DHEAS), which are immediate precursors for T and DHT production, or progesterone and estradiol, which are proximate T/DHT production precursor and metabolite, respectively. The information will facilitate definition of multifaceted involvement of SLCO transporters in androgen metabolism by prostate cancer, and will be critical for interpretation of findings in association of genotypes or expression levels with prostate cancer characteristics once Aim 1 and Aim 2 are completed.

Fig 2 . Steroids are different in the ability of competition for ^{3}H-T uptake analysis.

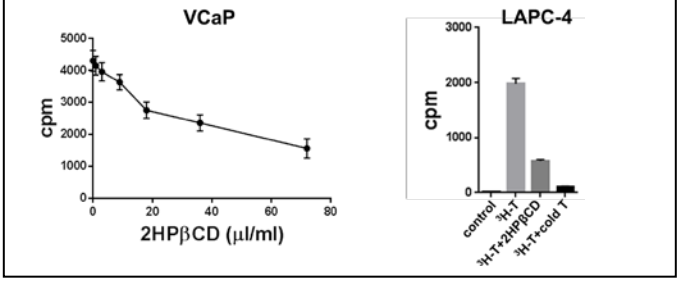


T	DHT	Progester -one	estradiol	ASD	DHEA	DHEAS
100%	100%	100%	100%	50%	0%	0%



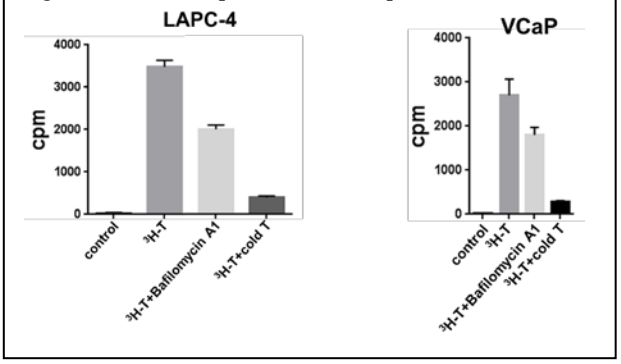
Two prostate cancer cell lines were used to in experiments on competition of steroids on T uptake (Figure 2). Excessive amount of non-radioactive steroids were added in the presence of 1 nM ^{3}H-T. ^{3}H-T uptake was measured using method established in Year 1. DHT, progesterone, estradiol were able to fully blocks uptake of T, indicating shared uptake mechanism for the 4 steroids. Adrenal androgens DHEA and DHEAS had no effect on T uptake, therefore, adrenal androgens uses different mechanisms to enter the cells. ASD partially blocked T uptake, indicating a shared mechanism with a much lower affinity to ASD.

Fig 3 . Possible location of uptake mechanism in cholesterol-rich cell membrane domain.



We also made progress in delineating molecular mechanisms for androgen uptake. First, we have identified subcellular localization of the uptake machinery, which exists in cholesterol-rich cell membrane domains (Figure 3). Prostate cancer cells were treated with 2HPβCD, a cholesterol carrier that is used for fluxing cholesterol out of cell membrane. Although treatment did not impact on cell viability, uptake of T was blocked. Second, treatment with vacuole ATPase inhibitor Bafilomycin A1 partly reduced T uptake (Figure 4). The results indicate that the uptake mechanism is an energy-consuming process, presumably an ATP-dependent mechanism that shares similarity with vacuole ATPase system.

Fig 4 . Testosterone uptake is an ATP-dependent mechanism.



The findings in Aim3 through Year 1 and Year 2 have been reported in the IMPACT meeting 2016 in a poster and an oral presentation. In summary, we have achieved all major goals set for Year 2. A number of new

findings have been made. Research proposed for all 3 specific aims are moving forward to Year 3 for completion.

What opportunities for training and professional development has the project provided?

Research activities in Year 2 continued to provide invaluable experience to Dr. Wu and Dr. Tang in interacting with the PCaP study. We have gained further insight in data management and infrastructure of the study. We completed genotyping and preliminary data analyses for Aim 1, which is the major task of the project in Year 2. During the process, Dr. Wu has gained first-hand experience in collaborating with Dr. Tang, a molecular epidemiologist, and Dr. Qianqian Zhu, a biostatistician who is an expert in genetic study. Working with Dr. Tang and Dr. Zhu offered Dr. Wu education in data analysis and association studies from perspectives of 2 disciplines that are distinctive in the methodologies and inference of data compared to Dr. Wu's background in basic research. Dr. Wu continued to learn from Dr. James Mohler and Dr. Gissou Azabdaftari to gain training and insight for critical review of data, and to align research activities with important clinical issues. The project also offered support to Dr. Wu to present research findings in the IMPaCT Meeting 2016. During the meeting our work has attracted interest from other investigators and provided opportunities for collaboration in order to bring forward the project and expand and deepened the research. The meeting also helped identify potential collaborators or advisors particularly important to interpreting the genotyping data and to bringing in expertise to strengthen Dr. Wu's research in health disparity of prostate cancer.

How were the results disseminated to communities of interest?

Results of Aim 3 were presented in IMPaCT 2016, in the format of a poster and a selected oral presentation.

What do you plan to do during the next reporting period to accomplish the goals?

The next reporting period will be the last year of this project. Since genotyping was the major task for the whole project, successful completion of this task in Year 2 is a critical achievement. Empowered by genotyping data, the experience we have gained in tissue section staining and androgen uptake studies, and the findings made, we expect to bring the project to completion by finishing all the remaining tasks on time. We will continue in Aim 1 for in-depth data analysis of the association of genotypes of the SLCO transporters with prostate cancer characteristics. For Aim 2 we will request TMAs from RPCI and PCaP and complete IHC and RNAScope staining for the SLCO transporters selected based on genotyping results and previous IHC/RNAScope results. The first SLCO transporters selected will include: SLCO2A1, SLCO3A1, SLCO4A1, and SLCO5A1. We will finish association studies on the expression levels of the transporters with prostate cancer characteristics. The data and findings in Aim 1 and Aim 2 will be combined and submitted for publications by the end of the project. For Aim 3 we will finish functional studies of the SLCO transporters by examining effects on androgen uptake, AR activity, and cell proliferation using cell models with over-expression and knockdown of SLCO transporters. The uptake mechanism and functional studies on the identified functional SNPs will be reported in 2 separate manuscripts.

4. IMPACT

What was the impact on the development of the principle discipline(s) of the project?

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGEs/PROBLEMS

Changes in approach and reasons for change.

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them.

In Year2, one incidence set back the progress and delayed completion of genotyping by nearly two month. The issue was caused by a failed kit that was used by the Genomics Core Facility at RPCI. The failed reagent was one of multiple packages provided by Illumina. Each individual package of the reagent was used on one 96-well plate for genotyping. The failed reagent caused failed genotyping of a whole plate that contains 92 DNA samples. The issue was resolved between the Core and Illumina, with the latter provided free reagent for a new round of genotyping. Consequently, we had to contact with PCaP to request DNA samples to replace the one on the failed 96-well plate. PCaP team was highly supportive to make the replacements available to us. Genotyping was carried forward without additional incidence.

Changes that had a significant impact on expenditures.

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents.

Nothing to report.

6. PRODUCTS

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Yue Wu, Ph.D. (2 cal months) – PD/PI

Li Tang, Ph.D. (1 cal month) – Co PD/PI

James Mohler, M.D. (0.1 cal month) - Co-Investigator

Gissou Azabdaftari, M.D. (1 cal month) – Co-Investigator

Qianqian Zhu, Ph.D. (1 cal month) – Co-Investigator

Elena Pop, M.D. (1 cal month) – Research Associate

Todd Parsons (2 cal months) – Technician

Rachel Pratt (1 cal month) – Technician

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Yes. Updated active other supports of Dr. Yue Wu (PI), Dr. Li Tang (co-PI), Dr. James Mohler (co-I), Dr. Gissou Azabdaftari (co-I), Dr. Qianqian Zhu (co-I), Dr. Elena Pop (co-I) and Dr. John Wilton (co-I) are presented as follows.

Changes in active support

Yue Wu
Pending to Active:
Title: Targeting Usage of Adrenal Androgens for Complete Androgen Deprivation Therapy (Wu)
Time Commitments: 0.60 calendar months
Supporting Agency: New York State Department of Health- DOH01-C30314GG-3450000
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Judith Epstein, Director Grants & Foundation Office, Elm & Carlton Streets, Research Studies Center Room 234, Buffalo, NY 14203, Judith.Epstein@RoswellPark.org
Performance Period: 12/01/2015-10/31/2017
Level of Funding: $130,430
Brief description of project's goals: The goal of this research is to discover if targeting the highly diverse ability of using different adrenal androgens for CaP cell production of T or DHT is critical to achieving complete ADT.
List of specific aims:
Aim 1. Determine the dynamic changes in the capability of CaP cells to use adrenal androgens for T/DHT production in response to castration
Aim 2. Identify candidate chemicals to block the usage of adrenal androgens to activate AR, and to test the feasibility of blocking the use of adrenal androgens to prevent tumor growth
Aim 3. Evaluate whether co-existing CaP cells that differ in androgen uptake or metabolic abilities synergistically use adrenal androgens for T or DHT production
Overlap: None

Title: Prostate-specific androgen transporters are the missing target for complete ADT (Co-Pis- Smith/Wu)
Time Commitments: 2.40 calendar months
Supporting Agency: NIH (1R01CA193829-01A1)
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Viviana Knowles, Grants Management Specialist, 9609 Medical Center Drive, West Tower, Bethesda, MD 20892, phone: 240-765-5157, 10nowles.knowles@nih.gov
Performance Period: 12/09/2015-11/30/2020
Level of Funding: $1,961,530
Brief description of project's goals: The goal of this research is to determine if interdiction of prostate endothelial cell-specific uptake and trans-cellular transport of circulating adrenal androgens through the blood-prostate barrier, will complement ADT to provide a curative/durable therapy for organ-localized and advanced prostate cancer.
List of specific aims:
Aim 1. Determine inter-patient variability in up-take and metabolism of circulating T and DHEA-S, expression profiles of genes associated with androgen uptake/metabolism in human pECs and CaP/pEpi cells, and the short-term effect of T-deprivation on these processes

Aim 2. Define the molecular mechanisms that mediate uptake, trans-cellular transport and efflux of circulating androgens in human pECs and pEpi cells, and confirmed in pECs with CaP
Aim 3. Determine whether interdiction of adrenal androgen usage by pEC and/or CaP/pEpi has the potential to enhance the therapeutic effect of T-deprivation (ADT)
Overlap: None

Li Tang
Active to Completed:
Title: Lifestyle and molecular factors of bone health in breast cancer survivors (PI: Kwan/Yao)
Time Commitment: 2% effort (0.24 calendar months)
Supporting Agency: NIH/NCI R01 CA166701A
Grants Officer: Catherine Alfano
Performance Period: 7/1/12 – 6/30/16
Level of Funding: $ 196,096
Brief Description of Project's Goals:
The overall goal is to investigate lifestyle factors, genetic polymorphisms, and serum biomarkers as predictive factors for adverse bone complications among postmenopausal women with breast cancer who took aromatase inhibitors in the Pathways Study.
List of Specific Aims:
1. To investigate the associations of modifiable lifestyle factors and risk of osteoporosis and fractures in postmenopausal women who received AI therapy for early-stage, HR-positive breast cancer.
2. To investigate the associations of germline genetic variations in estrogen and bone metabolism pathways and risk of osteoporosis and fractures in postmenopausal women who received AI therapy for early-stage, HR-positive breast cancer.
3. To investigate the associations of serum biomarkers, including BAP for bone formation and TRAP5b for bone resorption, six key regulatory cytokines (RANKL, OPG, IL1, IL6, TNFα, CSF), and 25-hydroxyvitamin D, and risk of osteoporosis and fractures in postmenopausal women who received AI therapy for early-stage, HR-positive breast cancer.
4. To develop a composite risk prediction model for AI-induced fractures that includes significant lifestyle factors, genetic variations, and serum biomarkers identified in Aims 1-3.
Overlap: None

James Mohler
Pending to Active:
Title: Network Lead Academic Participating Site Grant from the Roswell Park Cancer Institute (Adjei, Lele, Levine, Singh - PIs)
Time Commitment: 0.60 calendar months
Supporting Agency: NIH: NCI NCTN Program IU10 CA180866-01
Funding Agency's Procuring Contracting/Grants Officer: Margaret M. Mooney, Program Official, BG 9609 RM 5W412, 9609 Medical Center Drive, Rockville, MD 20850, phone 240-276-6560, mooneym@mail.nih.gov
Performance Period: 05/06/2014-02/28/2019
Level of Funding: $3,080,000
Brief description of project's goals: The aim of inter-Institutional cooperative clinical research is to advance our understanding of malignant diseases and, thereby, improve our ability to treat people afflicted with them. These aims are accomplished by resolving scientific questions of importance regarding cancer biology and therapy through the cooperation of selected Institutions that can pool their intellectual, technical, and patient resources. The rapid accumulation of clinical data and experience through cooperative research expedites progress in cancer therapy.

List of specific aims: The Roswell Park Cancer Institute has had a long tradition of contributing to the national cooperative groups over many decades. Those contributions have been scientific, administrative, and participatory (over 1200 patients have been enrolled in cooperative group trials over the last 5 years). This application summarizes the intent of its 4 Co-PIs (Levine/Adjei/Lele/Singh) and the membership of RPCI to sustain its commitment to the many strengths inherent to cooperative group research: therapeutic advances; a better understanding of the biology of cancer; cancer prevention; means to improve the quality of life of cancer patients; piloting of new drugs and radiology and radiation and surgical techniques; establishing the relevance of new cellular and molecular advances to the predictive, prognostic, and therapeutic approaches to patients; and the advancement of patient advocacy. Investigators at RPCI and its supporting staff fully recognize the essential importance of the timely and accurate submission of data and specimens to achieve these aims.
Overlap: None

Title: The Thoc1 Ribonucleoprotein as a Novel Biomarker for Prostate Cancer Treatment Assignment (Goodrich - PI)
Time Commitments: 1.20 calendar months
Supporting Agency: USAMRAA PC130746P1
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Lance Nowell, lance.l.nowell.civ@mail.mil, Phone: 301-619-1357
Performance Period: 09/15/2014-09/14/2017
Level of funding: $379,593 (partnering PI)
Brief description of project's goals: The central objective of this application is to test the utility of a novel molecular biomarker, *THOC1*, which may improve assignment of patients to appropriate therapy.
List of specific aims:
1. Characterize pThoc1 levels in independent cohorts of human prostate cancer radical prostatectomy specimens.
2. Characterize pThoc1 levels in a cohort of human prostate cancer patients on active surveillance.
3. Test whether pThoc1 or autoantibodies against pThoc1 can be detected in the blood of prostate cancer patients.

Overlap: None

Title: Deprive prostate cancer of DHEAS to prevent castration-recurrent prostate cancer (Wu – PI)
Time Commitments: 0.12 calendar months
Supporting Agency: NIH/NCI 1R21CA191895-01
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Viviana Knowles, 9609 Medical Center Drive, West Tower, Bethesda, MD 20892, phone: 240-276-5157, viviana.knowles@nih.gov
Performance Period: 09/17/2014-08/31/2017 (NCE)
Level of Funding: $419,884
Brief description of project's goals: This research seeks to address the racial differences in prostate cancer aggressiveness from a biological perspective.
List of specific aims:
1. Characterize the expression of STS and potential STS regulators in CRPC
2. Evaluate the value of targeting DHEAS usage by prostate cancer cells to prevent post-castration tumor growth
3. Identify DHEAS uptake mechanisms

Overlap: None

Title: Qualifying multi-transcript signatures for active surveillance in prostate cancer (Kim/Mohler - PIs)
Time Commitments: 0.60 calendar months
Supporting Agency: National Institutes of Health 1R01CA182438-01A1

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Not assigned yet
Performance Period: 09/01/2014-08/31/2019
Level of funding: $195,510 (sub contract)
Brief description of project's goals: The vast majority of men diagnosed with prostate cancer do not die of their disease, yet prostate cancer remains the second leading cause of cancer-death in men. We propose to qualify prognostic transcriptomic signatures to predict the risk of adverse prostate cancer pathology and disease progression using prostate needle biopsies from men considering active surveillance as a strategy to delay and even avoid the treatment of prostate cancer. A qualified test will help with treatment decisions at the time of prostate cancer diagnosis. Another objective addresses the glaring absence of well-established criteria for active surveillance in non-Caucasian men. We propose to qualify our signatures in African-American men. Qualified signatures of cancer severity will improve outcomes prediction and identify the most appropriate candidates for active surveillance, and ultimately reduce the public health burden of prostate cancer.
List of specific aims:
1. Qualify biomarkers to predict adverse pathology and progression using prostate biopsies in men considering active surveillance.
2. Test the effects of African-American ethnicity on the biomarker signatures.

Overlap: None

Title: Cholesterol Lowering Intervention for Prostate Cancer Active Surveillance/Jr. Faculty Award to Alliance NCORP Research Base – Pilot Project (Kim/Mohler - PIs)
Time Commitments: 0.60 calendar months
Supporting Agency: Cedars/NCI
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Subcontract with Cedars Sinai. Cedars-Sinai Medical Center, Attention: Margaret Jenkins, Administrative Program Coordinator Department of Surgery, Research Division, 8635 W. 3rd Street, Suite 973W, Los Angeles, CA 90048 margaret.jenkins@cshs.org
Performance Period: 04/01/2015 – 03/31/2017
Level of funding: $93,955 (sub contract)
Brief description of project's goals: The proposed research tests the hypothesis that intensive cholesterol lowering will decrease the growth rate of benign and malignant prostate epithelium. The proposed research could provide the data necessary to justify a phase III clinical trial to address one of the major problems in urologic oncology how to prevent the progression of low risk prostate cancer to provide men higher levels of confidence for selection of active surveillance.
Overlap: None

Title: A Small-Molecule Inhibitor of the Terminal Steps for Intracrine Androgen Synthesis in Advanced Prostate Cancer (Mohler)
Time Commitments: .975 calendar months
Supporting Agency: NCI-1R21CA205108-01
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Nicole Franklin, Grants Management Specialist, National Cancer Institute, 9609 Medical Center Drive, West Tower, Room 2W556, Bethesda, MD 20892 (regular mail), Phone: 240-276-5210, Email: nicole.franklin@nih.gov
Performance Period: 04/10/2016-04/09/2018
Level of Funding: $ 416,398
Brief description of project's goals: This research seeks to explore if a small-molecule inhibitor of the catalytic site shared by the five 3α−oxidoreductases will decrease T and DHT metabolism through the frontdoor and backdoor pathways.
List of specific aims:
1. Identify a candidate inhibitor against the catalytic site shared by the five 3α−oxidoreductases
2. Synthesize and test re-designed candidate inhibitors and conduct PK/PD and toxicity studies to produce a lead compound inhibitor of the five 3α−oxidoreductases

3. Determine whether the inhibitor of the 3α−oxidoreductases decreases tissue T and DHT levels and impairs CRPC growth

Overlap: None

Title: Understanding the Relative Contributions of and Critical Enzymes for the 3 Pathways for Intracrine Metabolism of Testicular Androgens in Advanced Prostate Cancer.
Time Commitments: 1.65 calendar months
Supporting Agency: DoD PC150326
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Tom Winter Grants Specialist, Assistance Agreements Branch 4 U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick, MD 21702 Cell 240-357-1590 Office 301-619-2665 Thomas.s.winter2.civ@mail.mil
Performance Period: 09/30/2016-09/29/2019
Level of funding: $660,315
Brief description of project's goals: This research seeks better understanding of intracrine androgen metabolism during ADT will identify new targets to reduce T and DHT production.
List of specific aims:

1. Determine the relative use of the 3 pathways for intracrine androgen metabolism in vitro, in vivo and in clinical specimens
2. Identify the principal androgen metabolism enzymes (i.e., 3α-oxidoreductases) responsible for primary backdoor DHT synthesis from androstanediol
3. Determine the requirements for SRD5A1-3 in the frontdoor pathway of DHT synthesis from T and its precursors and of SRD5A1 and HSD17B3 in the secondary backdoor pathway of DHT synthesis from androstenedione

Overlap: None

Title: The NF-kappaB-androgen Receptor Axis Drives Failure of Medical Therapy in Human Benign Prostatic Hyperplasia (Matusik)
Time Commitments: 0.30 calendar months
Supporting Agency: NIH/NIDDK Melissa Haney, Manager, Dept of Urologic Surgery, Vanderbilt University. 615-322-3172, Melissa.haney@vanderbilt.edu
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: not assigned
Performance Period: 09/16/2016 – 07/31/2021
Level of funding: $151,840 (sub)
Brief description of project's goals: NFB and AR signaling controls the failed response to 5ARIs in BPH.
List of specific aims:

1. Determine cross-talk between NFB and AR signaling to regulate failure of edical therapy
2. Determine the SRD5A isoforms contribution during resistance to medical therapy
3. Determine if failure of medical therapy is driven by NFB and/or AR-V7 in BPH patients. New insight into how BPH patients fail 5α-reductase inhibitors holds the promise to identify pathways to apply novel approaches to medical therapy in the treatment of BPH.

Overlap: None

Active to Completed:
Title: Prostate Cancer: Transition to Androgen Independence, Core A: Administration (Mohler – PI) No Cost Extension
Time Commitments: 1.16 calendar months
Supporting Agency: National Cancer Institute P01-CA77739
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Mark Kramer, Administrative Director, UNC Lineberger Comprehensive Cancer Center Campus Box 7295

102 Mason Farm Road, Chapel Hill, NC 27599-7295, Phone: (919) 966-0233, Fax: (919) 966-3015, mkramer@med.unc.edu
Performance Period: 04/01/2005-03/31/2015
Level of Funding: $25,546 (sub only)
Brief description of project's goals: Renewal of an administrative core that provides the leadership for the overall Program Project in the daily execution of administrative matters common to the three projects and ImmunoAnalysis and Tumor Management Core B.
List of specific aims:
The objective of the Administration Core A is to provide leadership, direction and administrative services for the purposes of enhancing research productivity and maintaining a stimulating research environment conducive to study of prostate cancer biology. Administration Core A will foster exchange of ideas and promote collaboration through its interactions with the Project Leaders and research groups. A major effort will be to encourage and facilitate collaboration in translational research among investigators within the Program Project and other investigators within or outside UNC-Lineberger Comprehensive Cancer and Roswell Park Cancer Institute. Administration Core A will have direct responsibility for organization and facilitation of the monthly research conferences and annual review of the Program Project by the 5 external consultants. Administration Core A will monitor activities of ImmunoAnalysis and Research Specimen Management Core B, in particular, and the entire program, in general, to improve the efficiency and effectiveness of the entire program.
Overlap: None

Title: Prostate Cancer: Transition to Androgen Independence, Core B: ImmunoAnalysis and Tumor Management (French – PI)
Time Commitments: 0.48 calendar months
Supporting Agency: National Cancer Institute P01-CA77739
Name and address of the Funding Agency's Procuring Contracting/Grants Officer:
Mark Kramer, Administrative Director, UNC Lineberger Comprehensive Cancer Center Campus Box 7295 102 Mason Farm Road, Chapel Hill, NC 27599-7295, Phone: (919) 966-0233, Fax: (919) 966-3015, mkramer@med.unc.edu
Performance Period: 04/01/2005-03/31/2015
Level of Funding: $110,440 (sub only)
Brief description of project's goals: Renewal of a core that serves two primary functions to the three projects: Core B is involved in all aspects of clinical specimen and prostate cancer xenograft management and Core B processes and stores the invaluable prostate biopsy specimens obtained from men with advanced prostate cancer prior to and at regular intervals after beginning androgen deprivation therapy.
List of specific aims:
The ImmunoAnalysis and Research Specimen Management Core B will provide 3 primary services to the Program Project.
1. Core B will provide high quality, reliable and cost-effective technical services to participants of the Program Project for immunohistochemistry and quantitative image analysis.
2. Core B will manage the research specimens critical to the conduct of the research proposed by the Program Project.
3. Core B will provide expertise in biostatistics and genitourinary pathology.
Overlap: None

Title: Role of Androgen Axis in the Racial Differences of Prostate Cancer Mortality (PI – Mohler)
Time Commitments: 1.20 calendar months
Supporting Agency: Department of Defense
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Ayi Ayayi, Contract Specialist U.S. Army Medical Research Acquisition Activity, MCMR-AAA-E, 820 Chandler Street, Fort Detrick, MD 21702-5014 Phone: (301) 619-4018 ayi.ayayi@us.army.mil
Performance Period: 09/30/2010-09/29/2014

Level of Funding: $153,671 (NCE)
Brief description of project's goals: The study will provide complete analysis of the androgen receptor and androgen-regulated genes and relate it to prostate cancer in a large sample of men to test whether racial differences in prostate cancer mortality may be due, in part, to racial differences in androgenic stimulation of prostate cancer. Greater androgenic stimulation of the African American prostate could explain the two-fold difference in prostate cancer risk and increased aggressiveness of clinical disease in African compares to Caucasian Americans.
List of specific aims:
The central hypothesis of the proposed research is that racial differences in the tissue androgen axis contribute to CaP aggressiveness. Greater androgenic stimulation of the African-American prostate may contribute to increased incidence of, and higher mortality rates from, CaP. Quantifying the androgen axis in a large number of men with CaP will determine whether or not CaP receives race-dependent differences in androgenic stimulation that may affect CaP outcome. In order to test the central hypothesis, we propose three specific aims:
1. Determine whether AR protein levels differ in CaP of African and Caucasian Americans
2. Determine whether AR protein levels correlate with proteins expressed from androgen-regulated genes (PSA, Nkx3.1, hK2, *TRMPRSS2/ERG* fusions)
3. Determine whether AR protein levels correlate with CaP growth rate, extent and tumor differentiation
Overlap: None

Title: Genetic variations in mitochondria and prostate cancer aggressiveness and progression in Caucasian and African American men (PI – Zhao)
Time Commitments: 0.60 calendar months
Supporting Agency: Department of Defense
Name and address of the Funding Agency's Procuring Contracting/Grants Officer:
Sherie Wesley, Research Contract Specialist, Legal Services Department, LEGAL SERVICES, Unit 537, P. O. Box 301439, Houston, Texas 77230-1439
Email: swesley@mdanderson.org
Phone: 713.794.1507
Fax: 713.792.6878
Performance Period: 07/01/2012-06/30/2015
Level of Funding: $48,261 (sub only)
Brief description of project's goals:
Objectives
The hypothesis is that genetic variations (sequence and copy number) in mtDNA are associated with prostate cancer aggressiveness at diagnosis and prostate cancer progression. The proposed study will represent the first study to address the roles of mtDNA variations in prostate cancer aggressiveness and progression as well as racial difference.
List of specific aims:
1. Evaluate whether genetic variations in mtDNA are associated with aggressive tumor characteristics of prostate cancer at diagnosis and progression of prostate cancer in CA and AA men, and whether the associations are different between CA and AA men.
2. Evaluate whether mtNDA CNVs are associated with aggressive tumor characteristics of prostate cancer at diagnosis and progression of prostate cancer in CA and AA men, and whether the associations are different between CA and AA men.
3. Exploratory Aim: Perform whole mitochondrial DNA sequencing to identify novel genetic variants in AA and CA prostate cancer patients.
Overlap: None

Title: PKN1 as a novel therapeutic target to block clinically relevant androgen action in prostate cancer (PI – Heemers)
Time Commitments: 0.24 calendar months

Supporting Agency: Roswell Park Alliance Foundation
Name and address of the Funding Agency's Procuring Contracting/Grants Officer:
Judith Epstein, Director Grants & Foundation Office, Roswell Park Cancer Institute, Elm & Carlton Streets, Research Studies Center Room 234, Buffalo, NY 14203, Judith.Epstein@RoswellPark.org
Performance Period: 04/02/2013 – 04/01/2014
Level of Funding: $50,000
Brief description of project's goals:
The RhoA effector PKN1 that is responsible for conveying androgen-responsiveness to SRF represents an attractive novel target to inhibit selectively clinically relevant androgen action downstream of AR
List of specific aims:
1. Determine the therapeutic consequences of inhibition or mutation of PKN1 using a PKN1 inhibitor and site-directed mutations of PKN1 in sites that are necessary for RhoA interaction, and a preclinical CaP xenograft model
2. Determine the clinical relevance of PKN1 using immunohistochemistry and tissue microarrays (TMAs) that contain 715 CaP and control tissues for which complete clinical and outcome data is available
Overlap: None

Title: A Phase I Study of Methylseleno-L-Cysteine in Prostate Cancer Patients (PI – Marshall)
Time Commitments: 0.18 calendar months
Supporting Agency: Northwestern University/NIH
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Bruce Elliott, Jr., PhD – Director, Office for Sponsored Research
Email: b-elliott@northwestern.edu **Phone:** 312-503-7955 **Fax:** 312-503-2234
Performance Period: 05/01/2011-06/30/2014
Level of Funding: $318,700
Brief description of project's goals: This project is a continuation of a previous 1-arm study of Methylseleno-L-Cysteine in prostate cancer patients. This study adds 3 cohorts of 13 subjects each.
List of specific aims: To determine the individual toxicity profiles of MSC, SeMet and selenite administered to cohorts of men daily for 12 weeks, with dose escalation with each successive cohort.
Overlap: None

Title: Serum response factor as a novel therapeutic target in prostate cancer (PI - Heemers)
Time Commitments: 0.30 calendar months
Supporting Agency: Department of Defense
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Ayi Ayayi, Contract Specialist U.S. Army Medical Research Acquisition Activity, MCMR-AAA-E, 820 Chandler Street, Fort Detrick, MD 21702-5014 Phone: (301) 619-4018 ayi.ayayi@us.army.mil
Performance Period: 07/15/2010-01/14/2014
Level of funding: $79,115
Brief description of project's goals: The proposed aims to test this hypothesis employ *in vitro* and *in vivo* preclinical models of PCa to determine the molecular mechanisms underlying androgen regulation of SRF/RhoA signalling and their potential as novel targets for therapeutic intervention.
List of specific aims: Androgen activation of SRF signaling is important for PCa cell proliferation and invasive potential and that the RhoA/SRF signaling pathway represents a novel therapeutic target downstream of AR action.
1. Mechanistically corroborate the involvement of RhoA signaling in androgen regulation of SRF target genes
2. Determine the molecular mechanism(s) by which androgens stimulate SRF signaling
3. Determine the therapeutic potential of targeting SRF signaling using preclinical PCa models
Overlap: None

Gissou Azabdaftari
Pending to Active:
Title: The Thoc1 Ribonucleoprotein as a Novel Biomarker for Prostate Cancer Treatment (W81XWH-14-1-0476) (PI, Mohler)
Time Commitments: 0.24 Calendar Months
Supporting Agency: DOD - Janet P. Kuhns
Performance Period: 09/15/2014 – 9/14/2017
Level of Funding: $379,593
Brief description of project's goals: A critical unresolved issue complicating the clinical management of prostate cancer is over treatment. Active surveillance for men newly diagnosed prostate cancer is a potential solution to this problem. However, far fewer men elect active surveillance than outcome data suggest should, likely because it is currently difficult to identify the small fraction of localized prostate cancers likely to progress.
List of specific aims:
4. Characterize pThoc1 levels in independent cohorts of human prostate cancer radical prostatectomy specimens.
5. Characterize pThoc1 levels in a cohort of human prostate cancer patients on active surveillance.
6. Test whether pThoc1 or autoantibodies against pThoc1 can be detected in the blood of prostate cancer patients.

Overlap: NONE

Title: Therapeutic Efficacy of Riluzole in Prostate Cancer (1R21CA181152-01A1) (PI, Koochekpour)
Time Commitments: 0.30 Calendar Months
Supporting Agency: NCI - Michael C. Alley
Performance Period: 07/01/2014 – 06/30/2017
Level of Funding: $221,589
Brief description of project's goals: The effect of Riluzole on (i) tumor growth in a subcutaneous castrate-resistant (CR) progression model and (ii) spontaneous metastatic ability of an orthotopic xenograft model.
List of specific aims:
Determine the effect of Riluzole on FAS expression and apoptotic markers in primary and metastatic tumors. In this Aim, we will be able to verify our in vitro data by examining the association between Riluzole treatment and FAS expression and fatty acid content in tumor xenografts. In addition, we will investigate the underlying mechanisms by which Riluzole downregulates FAS expression in PCa cells. These preclinical exploratory studies should verify our in vitro data and validate therapeutic efficacy of Riluzole and anti-GRM1 targeted therapy leading to the development of clinical trials using GRM1-blocking agents in PCa patients
Role: Co-Investigator (Pathologist)
Overlap: NONE

Title: Deprive Prostate Cancer of DHEAS to Prevent Castration-Recurrent Prostate Cancer (1R21CA191895-01) (PI, Wu)
Time Commitments: 0.60 Calendar Months
Supporting Agency: NCI
Performance Period: 09/17/2014-08/31/2016
Level of Funding: $229,028
Brief description of project's goals: This research seeks to address the racial differences in prostate cancer aggressiveness from a biological perspective.
List of specific aims:
Aim 1: Characterize the expression of STS and potential STS regulators in CRPC
Aim 2: Evaluate the value of targeting DHEAS usage by prostate cancer cells to prevent post-castration tumor growth
Aim 3: Identify DHEAS uptake mechanisms

Role: Co-Investigator (Pathologist)
Overlap: NONE

Title: The Prognostic Role of Circulating Tumor Cells in Clinically Localized Clear Cell Renal Cell Carcinoma (PI, Kauffman)
Time Commitments: 0.24 Calendar Months
Supporting Agency: Roswell Park Alliance Foundation - Judith Epstein
Performance Period: 09/24/2015 – 09/23/2016
Level of Funding: $50,000
Brief description of project's goals: This project focuses on clear cell renal cell carcinoma (ccRCC), which accounts for the vast majority of kidney cancer diagnoses and deaths. It tests the hypothesis that CTC detection in the perioperative setting of clinically localized ccRCC provides a reliable surrogate for metastatic relapse. Key features of this proposal include the novel use a) a multiple protein marker 'cocktail' to overcome historic challenges of single-marker analysis in RCC, and b) high resolution imaging-based visual confirmation of marker-positive and marker-negative cells.
List of specific aims:
Aim 1: Validate a multimarker 'cocktail' strategy and image-based flow-cytometry platform for detection and enumeration of CTC in ccRCC patients.
Aim 2: Determine the relation of perioperative CTC levels to ccRCC tumor histopathology and metastatic relapse.
Overlap: NONE

Title: Metabotropic Glutamate Receptor 1 in African American Prostate Cancer (1R21CA183892-01) (PI, Koochekpour)
Time Commitments: 0.30 Calendar Months
Supporting Agency: NCI - Elizabeth Woodhouse
Performance Period: 04/01/2014 – 03/31/2017
Level of Funding: $184,658
Brief description of project's goals: Data generated from this exploratory study will define biological and/or clinicohistopathological significance or relevance of GRM1 expression in AA-PCa and may prove useful in discriminating clinically or biologically aggressive tumors from indolent (non-aggressive) tumors and minimizing PCa disparity in AAs.
List of specific aims:
Aim 1: To determine the association between tissue expression of GRM1 and clinicohistopathological predictors or prognosticators of PCa progression or aggressiveness in AAs.
Aim 2: To determine the association between GRM1 expression levels and invasive and metastatic phenotypes in AA-PCa cells.
Overlap: NONE

Active to Completed:
Title: Prosaposin: A novel Biomarker for Prostate Cancer in African Americans (Koochekpour- PI)
Time Commitments: 1.20 calendar months
Supporting Agency: NCI/NIH (R01MD005824)
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Rajapakse, Nishadi (chandima.rajapakse@nih.gov)
Performance Period: 07/01/2011-06/30/2014
Level of Funding: $1,512,198.00
Brief description of project's goals: This is a translational project investigating the potential of PSAP as a biomarker of prostate cancer aggressiveness in 1300 African American serum and tissue samples.
List of specific aims:

1) Define the clinical significance of serum-PSAP as a marker of PCa progression or aggressiveness in African Americans
2) Determine the association between tissue expression of PSAP and clinical and histopathological predictors or prognosticators of PCa progression or aggressiveness in African Americans
3) Determine the association between PSAP and invasive and metastatic phenotypes in PSAP-overexpressed or -silenced African American PCa cells.
Overlap: None

Title: Does dietary antioxidant predict aggressiveness of prostate cancer? (Chun- PI)
Time Commitments: 0.60 calendar months
Supporting Agency: NCI
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Dr. Antje Harnisch, University of Connecticut, 438 Whitney Road Ext., Unit 1133. Storrs, CT 06269.
Performance Period: 03/14/2012-02/28/2014
Level of Funding: $156,263 (Subcontract)
Brief description of project's goals: This study will evaluate the expression of thioredoxin reductase-1 (TrxR1) in correlation with Gleason score and level of PSA as well as integrate clinical data to verify the role of this protein in prostate cancer and its potential role as a therapy target to delay or prevent prostate cancer.
List of specific aims:

1. Determine the impact of dietary TAC on aggressiveness of newly diagnosed PCa
2. Determine whether dietary TAC level of PCa patients is associated with antioxidant-redox status in plasma, urinary, and PCa tissue samples
3. Aim 3. Evaluate major dietary, sociodemographic, and lifestyle factors contributing to racial differences in dietary TAC of PCa patients

Overlap: None

Title: PKN1 as a novel therapeutic target to block clinically relevant androgen action in prostate cancer (Heemers- PI)
Time Commitments: 0.24 calendar months
Supporting Agency: Roswell Park Alliance Foundation
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Judith Epstein, Director Grants & Foundation Office, Elm & Carlton Streets, Research Studies Center Room 234, Buffalo, NY 14203, Judith.Epstein@RoswellPark.org
Performance Period: 04/02/13 – 04/01/14
Level of Funding: $50,000
Brief description of project's goals:
The RhoA effector PKN1 that is responsible for conveying androgen-responsiveness to SRF represents an attractive novel target to inhibit selectively clinically relevant androgen action downstream of AR
List of specific aims:

1. Determine the therapeutic consequences of inhibition or mutation of PKN1 using a PKN1 inhibitor and site-directed mutations of PKN1 in sites that are necessary for RhoA interaction, and a preclinical CaP xenograft model
2. Determine the clinical relevance of PKN1 using immunohistochemistry and tissue microarrays (TMAs) that contain 715 CaP and control tissues for which complete clinical and outcome data is available

Overlap: None

Qianqian Zhu
Pending to Active:
Title: NCOR2/SMRT Drives the Onco-Epigenome of Aggressive Prostate Cancer (W81XWH-14-0608)
Time Commitments: 0.30 calendar (PI-Campbell/Smiraglia)

Supporting Agency: DOD
Grants Officer: Peggi Lesnow
Performance Period: 7/29/14-6/30/17
Level of Funding: $636,370
Brief Description of Project's Goals: The objective of the current study is to define the evolution of the NCOR2/SMRT cistrome and its association with CpG region methylation in ADT-RCaP. We hypothesize that acute environmental and therapeutic stresses in CaP selects for cells in which the NCOR2/SMRT complex drives repressive histone modifications that trigger CpG methylation, at select loci, to generate stable and heritable silencing of subsets of genes.
List of Specific Aims:

1. To reveal the impact of the NCOR2/SMRT cistrome in ADT-RCaP.
2. To measure in vivo the interplay between NCOR2/SMRT and CpG methylation in the emergence of ADT-RCaP.
3. To correlate NCOR2/SMRT expression and CpG methylation with miRNA serum expression levels and clinical outcomes.

Overlap: None

Title: Genomic markers predicting tumor response to cytotoxic chemotherapy (1R01 CA202354-01)
Time Commitments: 0.00 calendar (PI-Demant)
Supporting Agency: NIH
Grants Officer: Sudhir B. Kondapaka; sudhir.kondapaka@nih.gov; (240) 276-5365
Performance Period: 12/1/15-11/30/17
Level of Funding: $50,000
Brief Description of Project's Goals: We propose to develop a novel way to determine in advance whether individual cancer patients will benefit from a therapy with a certain anti-cancer drug, or whether they should receive another drug, because their tumor is not likely to be suppressed by the drug considered as the first. The specific advantage of the method we propose is that it is based not only on the current knowledge of pharmacology of anti-cancer drugs, but can discover also reliable predictive factors that are based on novel mechanisms.
List of Specific Aims:

1. Determination of linkage of Tctr genes polymorphic between CcS-2 and CcS-9 will be performed by standard linkage methods in F2 hybrids using a whole polymorphic genome coverage.
2. The linkages detected in the previous experiment will be confirmed in subsequent backcrosses that will serve as starting points for production of congenic lines, each carrying a single Tctr gene, so the functions of each such gene could be investigated separately. However, these congenic lines cannot be completed within the time frame of this project.

Overlap: None

Title: b-catenin in vaccine-induced anti-tumor CD8 cell immunity (1R01CA198105-01)
Time Commitments: 0.30 calendar (PI-Jiang)
Supporting Agency: NCI
Grants Officer: Anthony Welch; Office: (301) 846-5691
Performance Period: 7/1/15-6/30/20
Level of Funding: $401,456
Brief Description of Project's Goals: The long-term goal is to develop strategies to block tumor-induced immunosuppression to augment CD8+ T cell immunity and improve cancer vaccine efficacy. The objectives in this application is to elucidate the underlying mechanisms of how tumors inhibit cross-priming through b-catenin in DCs, and validate blocking b-catenin signaling as a novel strategy to improve cancer vaccine efficacy.
List of Specific Aims:

1. To determine whether activation of ß-catenin in DCs suppresses anti- tumor CD8+ T cell immunity under diverse cancer vaccinations.
2. To elucidate the molecular mechanisms of how tumors inhibit cross-priming through ß-catenin in DCs.
3. To determine whether blocking ß-catenin pharmacologically improves cancer vaccine efficacy.

Overlap: None

Title: KLF9-dependent pathways in multiple myeloma drug resistance (1R01CA190533-01A1)
Time Commitments: 0.60 calendar (PI-Nikiforov)
Supporting Agency: NIH
Grants Officer: Neeraja Sathyamoorthy; neeraja.sathyamoorthy@nih.gov; Office: (240) 276-6220
Performance Period: 7/10/15-6/30/20
Level of Funding: $2,122,500
Brief Description of Project's Goals: KLF9-dependent pathways underlying cytotoxicity of BTZ and CFZ are unknown. In search for such pathways, we utilized ChIP-Seq and quantitative RT-PCR assays and discovered that KLF9 suppresses expression of genes that directly or indirectly decrease oxidative stress. Among KLF9 targets involved in response to oxidative stress, we identified two genes that demonstrated KLF9-, CFZ- and BTZ-dependent expression pattern and whose genetic or pharmacological inhibition partially recapitulates the effects induced in MM cells by BTZ or CFZ. Thus, we will test the hypothesis that partial depletion of KLF9 targets mediates cytotoxicity of BTZ and CFZ, while more efficient genetic or pharmacological inhibition of these targets reduces tumor burden and increases efficacy of BTZ or CFZ in a mouse model of MM.
List of Specific Aims:

1. Mechanisms of induction and the role of KLF9 in cytotoxicity CFZ and BTZ.
    a. We will determine whether cytotoxicity of CFZ depends on KLF9 to the same degree as cytotoxicity of BTZ.
    b. We will identify CFZ- and BTZ-dependent mechanisms of KLF9 induction and assess their role in cytotoxicity of these agents.
2. Functional role of KLF9 target genes in anti-myeloma cell activity of BTZ, CFZ, and KH. Using gain-and-loss of function approaches, we will identify.
    a. Whether TXNRD2 levels regulates CFZ- or BTZ-dependent oxidative stress and cytotoxicity.
    b. Whether AZIN1 levels regulates CFZ- or BTZ-dependent polyamine levels and cytotoxicity.
    c. The role of AZIN1 in cytostatic effects of KH in MM cells.
3. Suppression of MM cell tumor burden via inhibition of TXNRD2 and AZIN1. We will generate orthotropic MM cell xenografts in SCID mice and assess the tumor burden under the following conditions.
    a. Genetic inhibition of TXNRD2 or AZIN1.
    b. Treatment with AUR or KH
    c. Treatment with BTZ or CFZ in combination with (1) or (2).

Overlap: None

Title: Genetic variants, reproductive history, and breast cancer risk in African American women (1R03 CA192205-01A1)
Time Commitments: 0.60 calendar (PI-Yao)
Supporting Agency: NCI
Grants Officer: Damali Martin; damali,martin@nih.gov; Office: (240) 276-6746
Performance Period: 7/1/15-6/30/17
Level of Funding: $175,500
Brief Description of Project's Goals: By leveraging the existing exome array genotype data from a total of 8,350 AA breast cancer cases and healthy controls in the African American Breast Cancer Epidemiology and Risk (AMBER) Consortium, we propose to identify rare and low-frequency coding variants associated with reproductive aging.
List of Specific Aims:

1. To evaluate rare and low-frequency coding variants in the regions identified by previous genome-wide association studies for age at menarche and age at natural menopause.
2. To identify rare and low-frequency coding variants across the genome associated with reproductive aging phenotypes.

Overlap: None

Active to Completed:
Title: Pharmacoepigenetics of Noncoding RNAs in Breast Cancer (CCR12225973)
Time Commitments: 0.60 calendar **(PI-** Yao**)**
Supporting Agency: Susan Komen Foundation
Grants Officer: Anna Cabanes, PhD; 1-877-465-6636
Performance Period: 7/1/12-11/26/15
Level of Funding: $149,999
Brief description of project's goals: The goal of this study is to investigate genetic variations in noncoding RNAs and target genes in predicting the efficacy of breast cancer adjuvant chemotherapy based on the cooperative group trial SWOG S8897 and a population-based Pathways Study.
List of specific aims:

1. To identify germline variants in epigenetic ncRNAs associated with risk of recurrence in a group of 528 women treated with cyclophosphamide-based adjuvant chemotherapy in a prospective trial for early stage breast cancer. To determine if the associations are of prognostic or predictive value, similar analyses will be performed in 1,079 women followed-up without adjuvant treatment.
2. To validate the initial findings in a group of 800 early stage breast cancer patients selected from a prospective cohort and matched on cancer characteristics and treatment with patients from Aim 1.
3. To investigate the functional significance of identified variants in epigenetic ncRNAs using laboratory approaches.

Overlap: None

Title: Genetic Susceptibility to Unrelated Donor Stem Cell Transplant-Related Mortality (5R01HL102278-04)
Time Commitments: 2.40 calendar **(PI-** Hahn/Sucheston**)**
Supporting Agency: NIH
Grants Officer: Nancy DiFronzo; difronzon@nhlbi.nih.gov
Performance Period: 7/5/10-6/30/14
Level of Funding: $311,020
Brief description of project's goals: The goal is to improve survival after unrelated donor BMT used to treat blood diseases, which will enable more patients to receive this life- saving therapy
List of specific aims:

1. To undertake a genome-wide association study (GWAS) to map the independent and joint effects of recipient and donor genetic variation associated with TRM after HLA-matched unrelated donor BMT.
2. To determine the modifying effects of conditioning regimens on associations between recipient and/or donor genetic variants and TRM.
3. To replicate the top genetic associations in an independent cohort of 1,000 high resolution 10/10 HLA-matched BMT recipient-unrelated donor pairs.

Overlap: None

Elena Pop
Pending to Active:
Title: The Thoc1 Ribonucleoprotein as a Novel Biomarker for Prostate Cancer Treatment Assignment (Goodrich)

Time Commitments: 1.20 calendar months
Supporting Agency: USAMRAA PC130746P1
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Lance Nowell, lance.l.nowell.civ@mail.mil, Phone: 301-619-1357
Performance Period: 09/15/2014-09/14/2017
Level of funding: $379,593 (partnering PI)
Brief description of project's goals: The central objective of this application is to test the utility of a novel molecular biomarker, *THOC1*, which may improve assignment of patients to appropriate therapy.
List of specific aims:
1. Characterize pThoc1 levels in independent cohorts of human prostate cancer radical prostatectomy specimens
2. Characterize pThoc1 levels in a cohort of human prostate cancer patients on active surveillance.
3. Test whether pThoc1 or autoantibodies against pThoc1 can be detected in the blood of prostate cancer patients.

Overlap: None

Title: Deprive prostate cancer of DHEAS to prevent castration-recurrent prostate cancer (Wu)
Time Commitments: 1.80 calendar months
Supporting Agency: NIH/NCI 1R21CA191895-01
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Viviana Knowles, 9609 Medical Center Drive, West Tower, Bethesda, MD 20892, phone: 240-276-5157, viviana.knowles@nih.gov
Performance Period: 09/17/2014-08/31/2017 (NCE)
Level of Funding: $466,950
Brief description of project's goals: This research seeks to address the racial differences in prostate cancer aggressiveness from a biological perspective.
List of specific aims:
Aim 1. Characterize the expression of STS and potential STS regulators in CRPC
Aim 2. Evaluate the value of targeting DHEAS usage by prostate cancer cells to prevent post-castration tumor growth
Aim 3. Identify DHEAS uptake mechanisms
Overlap: None

Title: A Small-Molecule Inhibitor of the Terminal Steps for Intracrine Androgen Synthesis in Advanced Prostate Cancer (Mohler)
Time Commitments: 1.0 calendar months (year 2)
Supporting Agency: NCI-1R21CA205108-01
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Nicole Franklin, Grants Management Specialist, National Cancer Institute, 9609 Medical Center Drive, West Tower, Room 2W556, Bethesda, MD 20892 (regular mail), Phone: 240-276-5210, Email: nicole.franklin@nih.gov
Performance Period: 04/10/2016-04/09/2018
Level of Funding: $ 416,398
Brief description of project's goals: This research seeks to explore if a small-molecule inhibitor of the catalytic site shared by the five 3α−oxidoreductases will decrease T and DHT metabolism through the frontdoor and backdoor pathways.
List of specific aims:
4. Identify a candidate inhibitor against the catalytic site shared by the five 3α−oxidoreductases
5. Synthesize and test re-designed candidate inhibitors and conduct PK/PD and toxicity studies to produce a lead compound inhibitor of the five 3α−oxidoreductases
6. Determine whether the inhibitor of the 3α−oxidoreductases decreases tissue T and DHT levels and impairs CRPC growth

Overlap: None

Title: Genetic and Epigenetic Prostate Cancer-Related Alterations in Early-Onset disease in African American Men (Woloszynska-Read)
Time Commitments: 0.60 calendar months
Supporting Agency: NYSDOH
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Judith Epstein, Director Grants & Foundation Office, Elm & Carlton Streets, Research Studies Center Room 234, Buffalo, NY 14203, Judith.Epstein@RoswellPark.org
Performance Period: 11/01/2015-10/31/2017
Level of Funding: $ 130,430
Brief description of project's goals: Determine the relative frequency of genetic lesions found in prostate cancer in tumors from African Americans and European Americans. Determine the relative frequency of genetic lesions found in prostate cancer in tumors from African Americans and European Americans.
List of specific aims:
1. To determine the relative frequency of common genetic lesions found in prostate cancer in tumors from African Americans and European Americans.
2. To determine potentially relevant transcriptomic and methylomic differences in tumors from African Americans and European Americans.

Overlap: None

Title: Understanding the Relative Contributions of and Critical Enzymes for the 3 Pathways for Intracrine Mebolism (Mohler)
Time Commitments: 0.90 calendar months
Supporting Agency: DoD Idea Development Award
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Tom Winter Grants Specialist, Assistance Agreements Branch 4 U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick, MD 21702 Cell 240-357-1590 Office 301-619-2665 Thomas.s.winter2.civ@mail.mil
Performance Period: 04/01/2016-03/31/2019
Level of funding: $660,315
Brief description of project's goals:
Better understanding of intracrine androgen metabolism during ADT will identify new targets to reduce T and DHT production.
List of specific aims:
1. Determine the relative use of the 3 pathways for intracrine androgen metabolism in vitro, in vivo and in clinical specimens.
2. Identify the principal androgen metabolism enzymes (ie. 3a-oxidoreductases) responsible for primary backdoor DHT synthesis from androstanediol.
3. Determine the requirements for SRD5A1-3 in the frontdoor pathway of DHT synthesis from T and its precursors and of SRD5A1 and HSD17B3 in the secondary backdoor pathway of DHT synthesis from androstanedione.

Overlap: None

Active to Completed:
Title: Prostate Cancer: Transition to Androgen Independence, Core B: ImmunoAnalysis and Tumor Management (French – PI)
Time Commitments: 6.0 calendar months
Supporting Agency: National Cancer Institute P01-CA77739

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Mark Kramer, Administrative Director, UNC Lineberger Comprehensive Cancer Center Campus Box 7295, 102 Mason Farm Road, Chapel Hill, NC 27599-7295, Phone: (919) 966-0233, Fax: (919) 966-3015, mkramer@med.unc.edu
Performance Period: 04/01/2005-03/31/2015
Level of Funding: $110,440 (sub only)
Brief description of project's goals: Renewal of a core that serves two primary functions to the three projects: Core B is involved in all aspects of clinical specimen and prostate cancer xenograft management and Core B processes and stores the invaluable prostate biopsy specimens obtained from men with advanced prostate cancer prior to and at regular intervals after beginning androgen deprivation therapy.
List of specific aims:
Aim 1) Core B will provide high quality, reliable and cost-effective technical services to participants of the Program Project for immunohistochemistry and quantitative image analysis.
Aim 2) Core B will manage the research specimens critical to the conduct of the research proposed by the Program Project.
Aim 3) Core B will provide expertise in biostatistics and genitourinary pathology.
Overlap: None

Title: Role of Androgen Axis in the Racial Differences of Prostate Cancer Mortality (PI – Mohler)
Time Commitments: 6.0 calendar months
Supporting Agency: Department of Defense
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Ayi Ayayi, Contract Specialist, U.S. Army Medical Research Acquisition Activity, MCMR-AAA-E, 820 Chandler Street, Fort Detrick, MD 21702-5014 Phone: (301) 619-4018 ayi.ayayi@us.army.mil
Performance Period: 09/30/2010-09/29/2013
Level of Funding: $153,671
Brief description of project's goals: The study will provide complete analysis of the androgen receptor and androgen-regulated genes and relate it to prostate cancer in a large sample of men to test whether racial differences in prostate cancer mortality may be due, in part, to racial differences in androgenic stimulation of prostate cancer. Greater androgenic stimulation of the African American prostate could explain the two-fold difference in prostate cancer risk and increased aggressiveness of clinical disease in African compares to Caucasian Americans.
List of specific aims:
Aim 1) Determine whether AR protein levels differ in CaP of African and Caucasian Americans
Aim 2) Determine whether AR protein levels correlate with proteins expressed from androgen-regulated genes (PSA, Nkx3.1, hK2, TRMPRSS2/ERG fusions)
Aim 3) Determine whether AR protein levels correlate with CaP growth rate, extent and tumor differentiation
Overlap: None

John Wilton
Pending to Active:
Title: Deprive prostate cancer of DHEAS to prevent castration-recurrent prostate cancer (Wu)
Time Commitments: 0.60 calendar months
Supporting Agency: NIH/NCI (1R21CA191895-01)
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Viviana Knowles, 9609 Medical Center Drive, West Tower, Bethesda, MD 20892, phone: 240-276-5157, viviana.knowles@nih.gov
Performance Period: 09/17/2014-08/31/2016
Level of Funding: $419,884
Brief description of project's goals: This research seeks to address the racial differences in prostate cancer aggressiveness from a biological perspective.

List of specific aims:
Aim 1. Characterize the expression of STS and potential STS regulators in CRPC
Aim 2. Evaluate the value of targeting DHEAS usage by prostate cancer cells to prevent post-castration tumor growth
Aim 3. Identify DHEAS uptake mechanisms
Overlap: None

Title: Prostate-Specific Androgen Transporters are the Missing Target for Complete ADT (Smith/Wu)
Time Commitments: 0.30 calendar months
Supporting Agency: NIH (1R01CA193829-01A1)
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Viviana Knowles, Grants Management Specialist, 9609 Medical Center Drive, West Tower, Bethesda, MD 20892, phone: 240-765-5157, viviana.knowles@nih.gov
Performance Period: 12/09/2015-11/30/2020
Level of Funding: $1,961,530
Brief description of project's goals: This research seeks to determine if interdiction of prostate endothelial cell-specific uptake and trans-cellular transport of circulating adrenal androgens through the blood-prostate barrier, will complement ADT to provide a curative/durable therapy for organ-localized and advanced prostate cancer.
List of specific aims:
Aim 1. Determine inter-patient variability in up-take and metabolism of circulating T and DHEA-S, expression profiles of genes associated with androgen uptake/metabolism in human pECs and CaP/pEpi cells, and the short-term effect of T-deprivation on these processes
Aim 2. Define the molecular mechanisms that mediate uptake, trans-cellular transport and efflux of circulating androgens in human pECs and pEpi cells, and confirmed in pECs with CaP
Aim 3. Determine whether interdiction of adrenal androgen usage by pEC and/or CaP/pEpi has the potential to enhance the effect of T-deprivation (ADT)
Overlap: None

Title: A Small-Molecule Inhibitor of the Terminal Steps for Intracrine Androgen Synthesis in Advanced Prostate Cancer (Mohler)
Time Commitments: no salary requested, included as key personnel
Supporting Agency: NCI- 1R21CA205108-01
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Nicole Franklin, Grants Management Specialist, National Cancer Institute, 9609 Medical Center Drive, West Tower, Room 2W556, Bethesda, MD 20892 (regular mail), Phone: 240-276-5210, Email: nicole.franklin@nih.gov
Performance Period: 04/10/2016-04/09/2018
Level of Funding: $ 416,398
Brief description of project's goals: This research seeks to explore if a small-molecule inhibitor of the catalytic site shared by the five 3α−oxidoreductases will decrease T and DHT metabolism through the frontdoor and backdoor pathways.
List of specific aims:
Aim 1. Identify a candidate inhibitor against the catalytic site shared by the five 3α−oxidoreductases
Aim 2. Synthesize and test re-designed candidate inhibitors and conduct PK/PD and toxicity studies to produce a lead compound inhibitor of the five 3α−oxidoreductases
Aim 3. Determine whether the inhibitor of the 3α−oxidoreductases decreases tissue T and DHT levels and impairs CRPC growth
Overlap: None

Title: Understanding the Relative Contributions of and Critical Enzymes for the 3 Pathways for Intracrine Metabolism of Testicular Androgens in Advanced Prostate Cancer (Mohler)

Time Commitments: no salary, included as key personnel
Supporting Agency: DoD PC150326
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Tom Winter, Grants Specialist, Assistance Agreements Branch 4 U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick, MD 21702 Cell 240-357-1590 Office 301-619-2665 Thomas.s.winter2.civ@mail.mil
Performance Period: 09/30/2016-09/29/2019
Level of funding: $660,315
Brief description of project's goals: This research seeks to better understand intracrine androgen metabolism during androgen deprivation therapy (ADT) to identify new targets to reduce T and DHT production
List of specific aims:
Aim 1. Determine the relative use of the 3 pathways for intracrine androgen metabolism in vitro, in vivo and in clinical specimens.
Aim 2. Identify the principal androgen metabolism enzymes (ie. 3a-oxidoreductases) responsible for primary backdoor DHT synthesis from androstanediol
Aim 3. Determine the requirements for SRD5A1-3 in the frontdoor pathway of DHT synthesis from T and its precursors and of SRD5A1 and HSD17B3 in the secondary backdoor pathway of DHT synthesis from androstanedione.
Overlap: None

What other organizations were involved as partners?

Nothing to report.